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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,645	10/31/2000	Rainer Haas	100564-00035	6963

7590 03/27/2003

Arent Fox Kintner Plotkin & Kahn
Suite 600
1050 Connecticut Avenue
Washington, DC 20036

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,645	HAAS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-102* is/are pending in the application.

4a) Of the above claim(s) *59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-58 and 60-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed February 6, 2003. Applicants arguments presented in the response of February 6, 2003 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. This application contains claim 59 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of the nonelected claims and nonelected subject matter (e.g., SEQ ID NO: 2-4 in claims 57-59, 78, 92 and 93; non-elected regions in claim 60 and non-elected microorganisms in claim 62) or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claims 53-58 and 60-102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting clarithromycin resistance in H. pylori wherein the methods comprise detecting the presence of a A to G or A to C mutation at position 2058 of the 23S rRNA of H. pylori as indicative of resistance of H. pylori to clarithromycin, does not reasonably provide enablement for methods of detecting antibiotic resistance in any microorganism by detecting any mutation in any gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are very broadly drawn to methods for detecting macrolide antibiotic resistance in a microorganism wherein the methods comprise hybridizing a nucleic acid sample with a probe that is specific for any nucleic acid in any microorganism which is associated with resistance to

any antibiotic. The specification teaches (see, for example, page 6) six mutations in the 23S rRNA gene which result in resistance to the antibiotics chloramphenicol, clarithromycin, clinidamycin, erythromycin, linomycin and/or streptomycin in E.coli, P. acnes, M. pneumoniae, M. intracellular and/or H. pylori. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate what additional mutations in the 23S rRNA gene and in other genes will result in resistance to antibiotics. While the prior art teaches a limited number of additional genes which confer resistance to antibiotics, the teachings in the prior art of these genes is not representative of the broadly claimed genus of any gene having any mutation which confers resistance to any antibiotic in any microorganism. The claims include an incredibly large genus of mutations and genes which have not been adequately taught in the specification. The specification does not provide sufficient guidance as to how to identify

additional mutations and additional genes which confer resistance to antibiotics. To identify additional mutations associated with antibiotic resistance in microorganisms would require extensive analysis of a large genus of genes from a representative number of microorganisms for the presence of a mutation associated with resistance to any one of a large number of possible antibiotics. Such analysis is considered to be undue. The specification does not teach any mutations in any non-23S rRNA genes which confer resistance to antibiotics in Helicobacter. As set forth on page 6 of the specification, the specified 23S rRNA mutations confer resistance to different antibiotics in different microorganisms. For example, the 2058 mutation in the 23S rRNA confers resistance to clarithromycin in H. pylori, but confers resistance to erythromycin in M. pneumoniae. Accordingly, there is no predictable means for determining which mutations confer resistance to which antibiotics in a given microorganism. While the specification exemplifies methods which analyze the 23S rRNA for the presence of mutations at positions 2032, 2057, 2058, 2059, 2503 or 2611 in 5 microorganisms, only the mutation at position 2058 has been shown to confer antibiotic resistance H. pylori. The 2058 mutation has not been shown to confer resistance to any additional antibiotics in H. pylori and the 2058 mutation has not been shown to confer antibiotic resistance to any additional species of Helicobacter. The specification has not established that the stated mutations confer resistance to all antibiotics or that these mutations confer antibiotic resistance in all microorganisms. The ability to establish a correlation between the presence of a mutation and the occurrence of antibiotic resistance is highly unpredictable and can only be determined through extensive, random, trial and error

experimentation. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

4. **RESPONSE TO ARGUMENTS:**

In the response of February 6, 2003, Applicants stated that the rejection had been overcome because the claims had been amended to clarify that the present invention detects macrolide resistance in microorganisms. However, this amendment and Applicants comments do not address any of the points set forth in the rejection. The amendment to recite methods for detecting macrolide antibiotic resistance does not limit the claims with respect to the genus of mutations that are to be detected as indicative of macrolide antibiotic resistance. Applicants state that mutations in the 23S rRNA lead to antibiotic resistance in several organisms such as streptococci. However, the elected invention is not drawn to methods which detect macrolide antibiotic resistance in streptococci. Rather, the elected invention is limited to methods for detecting antibiotic resistance in Helicobacter. Furthermore, the showing at pages 5-7 of the specification is not representative of the breadth of the claims which includes detecting any type of macrolide antibiotic resistance in any microorganism by detecting any mutation in any gene that is associated with macrolide antibiotic resistance.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 92, 93 and 101 are rejected under 35 U.S.C. 102(a) as being anticipated by Pina (Journal of Clinical Microbiology (November 1998) 36(11): 3258-3290) .

It is noted that the present claims are entitled to the filing date of May 21, 1999. It is further noted that a certified translation of the foreign priority documents has not been provided

Pina teaches an oligonucleotide comprising 14 nucleotides of present SEQ ID NO: 1, wherein said probe can be used to detect antibiotic resistance (see page 3286-3287).

SEQ ID NO: 1: 5'-CGGGTCTTCCCGTCTT-3'

Pina (p43G): 5'- GGTCTTCCCGTCTTG-3'

With respect to claim 93, Pina further teaches labeling said nucleic acid with a biotin moiety (page 3286). Pina also teaches the use of this probe with wild-type probes.

RESPONSE TO ARGUMENTS:

In the response of February 6, 2003, Applicants state that a certified translation will be filed to overcome this rejection. However, the certified translation has not yet been received by the Office and thereby the rejection is maintained for the reasons of record.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 86-91 and 94-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morotomi (Journal of Clinical Microbiology (1989) 27: 2652-2655) in view of the Strategene Catalog (1988).

Morotomi teaches methods for detecting Campylobacter pylori, also known as Helicobacter pylori. The methods of Morotomi comprise growing C. pylori in a "presumptive medium", detecting the presence of C. pylori using a probe specific to the 16S rRNA of C. pylori (page 2653), and assaying bacterial cultures via the urease test using media containing a urease indicator. It is a characteristic of the medium that it contains a nitrogen source. Accordingly, the method of Morotomi requires a "presumptive medium", a means for typing a microorganism, and

an urease indicator present in a presumptive medium. Morotomi does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of Morotomi in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect C.pylori/H. pylori.

7. **RESPONSE TO ARGUMENTS:**

In the response of February 6, 2003, Applicants state that Morotomi does not teach reagent kits for determining macrolide antibiotic resistance in microorganisms in situ. However, the recitation of "for determining macrolide antibiotic resistance in microorganims by in-situ hybridization" merely sets forth the intended use or purpose of the claimed kits, but does not limit the scope of the claims. As stated in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999), if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then

the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation".

8. Claims 86-90 and 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pina in view of the Strategene Catalog (1988).

Pina teaches methods for detecting H. pylori. The methods of Pina comprise growing H. pylori in a "presumptive medium", detecting the presence of H. pylori using a probe to the 23S rRNA of H. pylori which detects the presence of the A2143G mutation (which is known in the art to be identical to the present A2058G mutation- the nucleotide position being different based on the numbering system utilized), and assaying bacterial cultures for their resistance to clarithromycin (see, pages 3285-3286). It is a characteristic of the medium that it contains a nitrogen source. Accordingly, the method of Pina requires a "presumptive medium", a nucleic acid probe associated with antibiotic resistance, and a means for typing an organism and detecting resistance to the antibiotic clarithromycin. It is noted that clarithromycin is considered to be an "indicator substance." Pina does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time

the invention was made to have packaged the reagents required to practice the method of Pina in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect antibiotic resistant strains of H. pylori.

RESPONSE TO ARGUMENTS:

In the response of February 6, 2003, Applicants state that a certified translation will be filed to overcome this rejection. However, the certified translation has not yet been received by the Office and thereby the rejection is maintained for the reasons of record. Applicants further state that the Stratagene catalog does not teach a reagent kit for determining macrolide antibiotic resistance. However, the Stratagene Catalog was not cited for teaching reagent kits for determining macrolide antibiotic resistance. Rather, the Stratagene Catalog was cited for its teachings regarding the packaging of reagents in a kit.

9. Claim 90, 91, 98-100 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pina in view of the Strategene Catalog (1988) and further in view of Morotomi.

The teachings of Pina and the Stratagene catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator .

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

RESPONSE TO ARGUMENTS:

In the response of February 6, 2003, Applicants state that a certified translation will be filed to overcome this rejection. However, the certified translation has not yet been received by the Office and thereby the rejection is maintained for the reasons of record. Applicants further state that neither Morotomi or the Stratagene catalog teach a reagent kit for determining macrolide antibiotic resistance. However, these references were not cited for teaching reagent kits for determining macrolide antibiotic resistance. Rather, the Stratagene catalog was cited for its teachings regarding the packaging of reagents in a kit and Morotomi was cited as teaching that H. pylori may be detected using a urease indicator.

10. Claims 53-58, 60-85 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pina in view of Amann.

It is noted that the present claims are entitled to the filing date of May 21, 1999. It is further noted that a certified translation of the foreign priority documents has not been provided

Pina teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Pina teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin . It is noted that the mutation in Pina is referred to therein as the "2143 mutation". However, this mutation is known in the art to be identical to the present mutation at position 2058. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori. The reference teaches that the 2058 mutation can be detected by first amplifying a sample nucleic acid using PCR and then using a probe to detect the presence of the

mutation in the amplified sequences. Pina does not teach detecting the 2058 mutation by performing in situ hybridization.

Amann teaches methods for detecting the presence of a mutation in bacterial DNA. In the methods of Amann, intact microbial cells are contacted with a nucleic acid probe and subjected to hybridization (see page 746). The in situ hybridization method of Amann allows one to effectively detect the presence of a single point mutation in the bacterial genome (page 765).

In view of the teachings of Amann, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pina so as to have detected the 2058 mutation by whole-cell in situ hybridization in order to have provided a highly effective and more rapid means for detecting clarithromycin resistance in H. pylori.

Pina teaches obtaining the H. pylori from patient samples and growing H. pylori in a "presumptive medium" containing an indicator, a nitrogen source, and a reducing agent cysteine. With respect to claim 64, Pina does not teach analyzing the sample without culturing. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the H. pylori sample could be directly analyzed by hybridization without culturing because Amann teaches that the whole-cell in situ hybridization method is effective for detecting a single cell. One of ordinary skill in the art would have been motivated to have omitted the culturing step in order to have provided a more rapid means for detecting clarithromycin resistance in H. pylori.

With respect to claim 68, Amann teaches fixing the cells prior to performing in situ hybridization. With respect to claim 78 and 102, Pina teaches a probe that differs from present

SEQ ID NO: 1 in that it is missing three 5' nucleotides and contains an additional 3' nucleotide (see page 3286-3287):

SEQ ID NO: 1: 5'-CGGGTCTTCCCGTCTT-3'

Pina (p43G): 5'- GGTCTTCCCGTCTTG-3'

Pina also teaches that the sequence of the H. pylori 23S rRNA was well known in the art (page 3286). Further, Amann teaches that the use of oligonucleotide probes of 15 to 25 nucleotides (page 763). Given the teachings of Amann of generating probes of a length up to 25 nucleotides, it would have been obvious to one of ordinary skill in the art that additional probes could be generated which are of a longer length and which would comprise the full length sequence of SEQ ID NO: 1. In the absence of evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to have generated additional probes of 17 or 18 nucleotides complementary to the stated region.

Amann teaches using multiple probes simultaneously. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, including the wild-type probe, in order to have detected clarithromycin sensitivity in H. pylori or to detect other mutations in H. pylori. In reference to claim 21, Amann teaches the use of genus and species specific probes. It would have been further obvious to one of ordinary skill in the art to have included a genus or species specific probe in order to have confirmed the identity of the organism. Pina also teaches that H. pylori can be microscopically and teaches quantitatively detecting clarithromycin resistance (page 3285-3286).

11. **RESPONSE TO ARGUMENTS:**

In the response of February 6, 2003, Applicants state that a certified translation will be filed to overcome this rejection. However, the certified translation has not yet been received by the Office and thereby the rejection is maintained for the reasons of record. Applicants further state that Amann does not teach using the in situ hybridization method for the detection of antibiotic resistance. However, Amann was not cited for teaching the use of in situ hybridization for the detection of macrolide antibiotic resistance. Rather, Amann was cited for its teachings of in situ hybridization using species and genus specific probes to detect the presence of a mutation in a microorganism. Applicants argue that regions of accessibility vary greatly and that not all regions will be accessible to a probe. It is asserted that the teachings of Amann would lead one away from the use of in situ hybridization to detect mutations associated with macrolide antibiotic resistance. These arguments have been fully considered but are not persuasive. It is unclear as to how on the one hand Applicants can argue that they are enabling for methods which detect any type of macrolide antibiotic resistance in any microorganism by detecting any mutation in any gene associated with macrolide antibiotic resistance and yet on the other hand assert that it is highly unpredictable as to whether a probe will be able to effectively bind to a target region to allow for the detection of a mutation. Applicants have not provided any teachings in their specification which would distinguish the claimed method over that of Amann. No specific guidance has been provided to overcome any of the obstacles asserted by Applicants. Further, Amann teaches regions of the rRNA which are accessible for hybridization and provides the

guidance to select additionally probes that allow for single-mismatch discrimination (see, for example, page 765) and thereby the ordinary artisan would have had more than a reasonable expectation of success of generating additional probes that could be used for in situ hybridization to detect point mutations in H. pylori.

Applicant's further assert that the claimed method is distinct over that of Amann because the claimed method is carried out with complex biological samples, whereas the method of Amann is carried out using cultivated and isolated microorganisms. However, Applicants are arguing limitations that are not recited in the claims. The claims do not require the direct use of a complex biological sample. Rather, the claims recite the claim language of comprising and may thereby include any number of purification steps. Furthermore, the claims as written also specifically include methods in which the microorganism is cultured prior to analysis.

12. Claims 53-58, 60-85, 92, 93, 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic (Antimicrobial Agents and Chemotherapy (Feb 1996) 40: 477-480) in view of Amann (Journal of Bacteriology (Feb 1990) 172: 762-770).

Versalovic teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Versalovic teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori (see page 478). The reference teaches that the 2058 mutation can be detected by sequencing the nucleic acids of H. pylori. However, the reference does not teach detecting the 2058 mutation by performing in situ hybridization.

Amann teaches methods for detecting the presence of a mutation in bacterial DNA. In the methods of Amann, intact microbial cells are contacted with a nucleic acid probe and subjected to hybridization (see page 746). The in situ hybridization method of Amann allows one to effectively detect the presence of a single point mutation in the bacterial genome (page 765).

In view of the teachings of Amann, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Versalovic so as to have detected the 2058 mutation by whole-cell in situ hybridization in order to have provided a highly effective and rapid means for detecting clarithromycin resistance in H. pylori.

With respect to claims 66 and 67, Versalovic teaches obtaining the H. pylori from patient samples and growing H. pylori in a "presumptive medium" containing an indicator. With respect to claims 89, 90, 96 and 97, Versalovic teaches growing H. pylori in brain heart infusion agar containing fresh horse blood. It is a property of this media that it contains the reducing agent cysteine and a nitrogen source. With respect to claim 64, Versalovic does not teach analyzing the sample without culturing. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the H. pylori sample could be directly analyzed by hybridization without culturing because Amann teaches that the whole-cell in situ hybridization method is effective for detecting a single cell. One of ordinary skill in the art would have been motivated to have omitted the culturing step in order to have provided a more rapid means for detecting clarithromycin resistance in H. pylori. With respect to claims 68 and 69, Amann teaches fixing the cells prior to performing in situ hybridization. With respect to probes, Versalovic

teaches a 19 bp region of 23S rRNA containing the 2058 mutation and Amann teaches that the use of oligonucleotide probes of 15 to 25 nucleotides (page 763). Accordingly, it would have been obvious to one of ordinary skill in the art to have generated probes complementary to the regions set forth by Versalovic wherein said probes are 15-25 nucleotides in length in order to have provided probes useful for detecting the 2058 mutation. Probes complementary to the region set forth by Versalovic comprise at least 10 nucleotides of SEQ ID NO: 1. The sequence complementary to the region disclosed by Versalovic differs from present SEQ ID NO: 1 only in that it is missing a 3' T nucleotide. However, the sequence of the 23S rRNA of H. pylori was well known in the art at the time the invention was made. Given the teachings of Amann of generating probes of a length up to 25 nucleotides, it would have been obvious to one of ordinary skill in the art that additional probes could be generated which are of a longer length and which would comprise the full length sequence of SEQ ID NO: 1. In the absence of evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to have generated additional probes of up to 25 nucleotides complementary to the region. Amann also teaches using multiple probes simultaneously. Accordingly, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, including the wild-type probe, in order to have detected clarithromycin sensitivity in H. pylori or to detect other mutations in H. pylori.

Further, Amann teaches the use of genus and species specific probes. It would have been further obvious to one of ordinary skill in the art to have included a genus or species specific

probe in order to have confirmed the identity of the organism. It is noted that Versalovic teaches examining H. pylori microscopically (page 477) and quantitatively detecting clarithromycin resistance (page 478).

13. **RESPONSE TO ARGUMENTS:**

In the response of February 6, 2003, Applicants state that Amann teaches away from and is using in situ hybridization to detect point mutations and that one of skill in the art would not have had a reasonable expectation of applying the in situ hybridization method of Amann to the detection of mutations associated with macrolide antibiotic resistance. However, as discussed above, these arguments are not consistent with Applicants assertion that they are enabling for methods which detect any type of macrolide antibiotic resistance in any microorganism by detecting any mutation in any gene associated with macrolide antibiotic resistance and yet on the other hand assert that it is highly unpredictable as to whether a probe will be able to effectively bind to a target region to allow for the detection of a mutation. Applicants have not provided any teachings in their specification which would distinguish the claimed method over that of Amann. No specific guidance has been provided to overcome any of the obstacles asserted by Applicants. Further, Amann does not teach away from the use of in situ hybridization to detect single mutations. Amann teaches that it is in fact possible to detect single mutations. In particular, the reference states that "it was nevertheless possible to distinguish between strains that differed by a single mismatch." While Amann acknowledges that not all probes will be effective, the reference states that additional probes can be determined empirically. In view of the fact that Amann

provides the guidance for performing in situ hybridization for the detection of point mutations, the ordinary artisan would have had more than a reasonable expectation of success of generating additional probes that could be used for in situ hybridization to detect point mutations in H. pylori.

14. Claims 86-90 and 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic (Antimicrobial Agents and Chemotherapy (Feb 1996) 40: 477-480) in view of Amann (Journal of Bacteriology (Feb 1990) 172: 762-770) in view of the Stratagene catalog.

The teachings of Versalovic and Amann are presented above. The combined references teach a method which requires the use of a 23S rRNA probe specific for the 2058 mutation of H. pylori, a presumptive medium, and an indicator substance for detecting antibiotic resistance. Versalovic does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of Versalovic in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect antibiotic resistant strains of H. pylori.

15. **RESPONSE TO ARGUMENTS:**

In the response of February 6, 2003, Applicants traverse this rejection for the same reasons discussed in paragraph 13 above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

16. Claims 91 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Amann and the Stratagene catalog and further in view of Morotomi.

The teachings of Versalovic, Amann and the Stratagene catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator .

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

17. **RESPONSE TO ARGUMENTS:**

In the response of February 6, 2003, Applicants traverse this rejection for the same reasons discussed in paragraph 13 above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

18. THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 53-58 and 60-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53-58 and 60-85 are indefinite. The claims are drawn to methods for detecting macrolide antibiotic resistance, yet recite a final step of detecting hybridization as indication of antibiotic resistance. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for detecting only macrolide antibiotic resistance methods for detecting any type of antibiotic resistance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 24, 2003

CARLA J. MYERS
PRIMARY EXAMINER